

## REMARKS

Existing claims 1-64 are pending in the application and claims 1-23, 26, 44-50, and 61-64 are currently under examination on their merits. Claims 1-12, 17, 22, 23, 26, 44, 45, 47, 48, 50, 61, 63 and 64 are being amended, as shown above. Withdrawn claims 24, 25, 27 and 60 are being cancelled, while new claims 65 through 68 are being added.

Where appropriate, the existing claims drawn to isolated protein complexes are being amended to indicate that the two constituent proteins interact to form the protein complex. Applicants have also amended the claims to improve clarity, consistency, and readability.

New dependent claims 65 through 68 are being added to better protect the instant invention. These new claims, which depend from either claim 1 or claim 12, are drawn to isolated protein complexes comprising Tsg101 fragments that either (a) consist essentially of a UEV domain or (b) comprise a portion of Tsg101 having no more than 207 contiguous amino acid residues, further comprising a UEV domain. Support for these new claims is found in the specification as filed. In particular, the specification teaches that “the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions” on page 38 (second paragraph) and “the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)” in the paragraph bridging pages 34-35. It is believed that no fees are required for the examination of these four new dependent claims since an equal number of withdrawn dependent claims are being cancelled.

Applicants respectfully submit that the proposed amendments to the existing claims, either place the claims in condition for allowance, or put the claims in better condition for appeal. Consequently, entry of the proposed amendments, as well as entry of the new dependent claims, is respectfully requested.

In accordance with 37 C.F.R. 1.121(f), Applicants submit that none of the proposed amendments adds new matter to the Application.

### **Withdrawn Rejections:**

Applicants acknowledge with gratitude the withdrawal of the rejection of claims 1-8, 12-15, 17-20, and 33 under 35 USC § 102(b) in view of *Ott*, as well as the withdrawal of the rejection of claims 9-11, 16, 21 and 23 under 35 USC § 103(a) in view of *Ott*, and in further view of *Desai*.

### **Maintained Rejections:**

#### **Claim Rejections under 35 USC § 112, second paragraph**

Claims 1-23 and 44-50 stand rejected under 35 USC § 112, second paragraph, for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter which Applicants regards as his invention. In particular, the Office Action alleges: (a) “the metes and bounds of the terms “homologue”, and “fragment” are not clear;” (b) that inclusion of the phrase “capable of interacting with” does not “require that an interaction take place;” and (c) inclusion of functional language into the claims does not solve the problem because “there is not a specific region of both proteins of the pair that define the interaction.” Applicants respectfully traverse and offer the following amendments and arguments.

As a first matter, in deference to one aspect of the Examiner’s rejection, Applicants have replaced the previously employed phrase “capable of interacting with” with the phrase “that interacts with,” in the amended claims. Applicants reiterate, as asserted previously, this functional language, in combination with recited structural features (i.e., percent identity to the native proteins comprising functional domains that were known in the art at the time the invention was made) helps to further define the already clear meaning of the terms “homologue” and “fragment” to one skilled in the art.

As a second matter, the Board of Patent Appeals and Interferences (the Board) has established:

In rejecting a claim under the second paragraph of 35 USC 112, it is incumbent on the Examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain **with a reasonable degree of precision and particularity** the particular area set out and circumscribed by the claims.

*Ex parte Wu*, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989), emphasis provided.

Thus, according to *Ex parte Wu*, one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, need not ascertain with **absolute** precision and particularity the particular area set out and circumscribed by the claims. In other words, in the instant case the claims need not recite the exact particulars of “fragments” and “homologues” and “homologues of fragments” of the interacting proteins of the isolated protein complexes.

Further, according to the MPEP:

When the Examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the Examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.

*MPEP* 2173, Original 8<sup>th</sup> Ed., Rev. 2, May 2004, p. 2100-205, emphasis in original.

If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim **so as to understand how to avoid infringement**, a rejection of the claims under 35 U.S.C. 112, second paragraph, would be appropriate.

*MPEP* 2173, Original 8<sup>th</sup> Ed., Rev. 2, May 2004, p. 2100-205, emphasis provided.

Applicants respectfully submit that the passages cited above indicate that to be patentable under 35 U.S.C. § 112, second paragraph, claims need not define the patentable subject matter with absolute particularity and distinctness, but only with a reasonable degree of particularity and distinctness. Further, because of the functional limitations incorporated into the pending claims, Applicants assert that a person of ordinary skill in the art would understand that they are infringing the claims, as amended herein, if they were to prepare an isolated protein complex comprising a first protein interacting with a second protein, wherein the first protein is Tsg101, or a fragment thereof comprising a UEV domain, or a homologue thereof, having an amino acid sequence that is at least 75% identical to that of Tsg101 or said fragment, and wherein the second protein is HIV GAG, GAGp6, or a fragment thereof comprising a late domain, or a homologue thereof having an amino acid sequence that is at least 50% identical to that of HIV GAG, or GAGp6, or a said fragment. Applicants further assert that there is nothing in this enterprise (of preparing an isolated protein complex as described) that would be unclear or confusing to the skilled artisan.

As a third matter, the Federal Circuit has declared that the test for definiteness under 35 U.S.C. 112, second paragraph, is whether “those skilled in the art would understand what is claimed when the claim is read in light of the specification.” *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088, (Fed. Cir. 1986).

The instant Office Action alleges that the metes and bounds of the terms “homologue” and “fragment” are not clear. Applicants respectfully disagree because, not only does the specification provide definitions of the terms “homologue” and “fragment” (in the paragraph bridging pages 11 and 12, and in the next-to-last paragraph on page 9, respectively) that include the requirement that such homologues and fragments interact to form protein complexes, but these terms, especially as used in reference to interacting proteins, were part of the standard vernacular of skilled artisans at the time the instant invention was made. In other words, the phrases “a homologue of Tsg101 that interacts with HIV GAGp6 and has an amino acid sequence at least about 75% identical to Tsg101” and “a fragment of GAGp6 that comprises a late domain and interacts with Tsg101” have clear meaning to one skilled in the art, and hence the metes and bounds of such terms would be clear.

As a further point, Applicants note that the Examiner has presented no evidence, or argument based upon logic to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain, with a reasonable degree of precision and particularity, the meaning of the terms “homologue” and “fragment.” The Examiner has merely stated that the metes and bounds of the term “homologue” and “fragment” are not clear. Consequently, the Examiner has not met his burden of providing evidence of a *prima facie* case to support the rejection of claims 1-23 and 44-50 under 35 USC § 112, second paragraph.

Curiously, the instant Office Action (page 4, 1<sup>st</sup> paragraph) alleges that the inclusion of functional language does not help in defining the metes and bounds of the terms “homologue” and “fragment,” because “there is not a specific region of both proteins of the pair that define the interaction.” In response, Applicants note that while the claims were intentionally written with a broader scope, the specification teaches that: “the inventors of the present invention discovered that **the first 14 amino acid residues**

**of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)”** (Specification, paragraph bridging pages 34-35); and **“the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions”** (Specification, page 38, second paragraph).

In view of these passages of the specification, Applicants respectfully remind the Examiner that: [t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether “those skilled in the art would understand what is claimed **when the claim is read in light of the specification.**” *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088, (Fed. Cir. 1986). (MPEP 2173.04, p. 2100-206, Original 8<sup>th</sup> Ed., Rev. 2, May 2004).

While the terms “homologue” and “fragment” do impart breadth to the pending claims, Applicants note that they purposefully included these terms in order to draft their claims with sufficient scope to fully encompass (and protect) what they regard as their invention. Applicants also note that the CCPA has ruled that inventors are entitled to claim their invention broadly, for in *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work ... would not serve the constitutional purpose of promoting progress in the useful arts.

Further, while the inclusion of the terms “homologue” and “fragment” do impart breadth to the pending claims, Applicants respectfully remind the Examiner that “[i]f the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, **then the claims comply with 35 U.S.C. 112, second paragraph**”(MPEP 2173.04, Original 8<sup>th</sup> Ed., Rev. 2, May 2004, p. 2100-207; emphasis provided); for “[b]readth of a claim is not to be equated with indefiniteness.” (*In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1071); emphasis provided).

In summary, Applicants respectfully assert that (a) in view of the definitions provided in the specification, and the functional language incorporated into the claims,

the meaning of the terms “homologue” and “fragment” in the pending claims would have been clear to one of skill in the art of molecular biology at the time the instant invention was made, (b) the Examiner has not met his burden of providing evidence to the contrary, and therefore has not made a proper *prima facie* case to support a rejection under §112, 2<sup>nd</sup> paragraph, and (c) while the terms “homologue” and “fragment” do impart breadth to the pending claims, they do not make the claims indefinite. Consequently, withdrawal of the rejections under 35 USC § 112, second paragraph is respectfully requested.

### **New Rejections:**

#### **Claim Rejections under 35 USC § 112, 1<sup>st</sup> paragraph – Written Description**

Claims 1-23, 26, 44-50 and 61-64 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse and offer the following arguments.

As a first matter, contrary to the assertions of the Examiner that “the applicants have only disclosed the sequences identified as GAG (449-500) and TSG101 (7-390) ... which are disclosed as interacting,” as indicated above, the specification teaches that: “the inventors of the present invention discovered that the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)” (Specification, paragraph bridging pages 34-35); and “[a]s discussed above, the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions” (Specification, page 38, second paragraph).

As a second matter, the Examiner has alleged (page 5, 1<sup>st</sup> paragraph) that: “The specification does not set forth the metes and bounds of all sequences that comprise the GAG late domain motif, there is not enough information about it in the literature either to guide the one of ordinary skill in the art to predict the undisclosed regions where the region may encompass or if they will bind.” In response, Applicants note that the:

1. The HIV late domain was defined by Leslie Parent and coworkers in 1995, and is described in the publication Parent *et al.*, *J. Virol.* 69(9):5455-5460, 1995, which was cited in the specification bridging pages 36-37.

2. Parent *et al.*, report (page 5459, bottom left column): “The portion of p6 most important for budding has been mapped to the first 12 residues, including the prolines at positions 10 and 11.”
3. Also in 1995, Mingjun Huang and coworkers reported in their publication that: “Our results indicate that p6 is required for efficient virus particle production from HeLa cells transfected with a full-length HIV-1 molecular clone and that a PTAP sequence, located between p6 residues 7 and 10, is critical for efficient virus particle production. The p6 defect [in virus particle production] occurs at a late stage in the budding process....”
4. Accordingly, at least 6 years prior to the filing of the instant application, the late domain was mapped to the N-terminus of p6, and was known to include the PTAP motif.
5. Since 1995, numerous other groups have studied the late domain of HIV GAGp6, and have reinforced the importance of the PTAP motif, and the N-terminal portion of p6, in HIV budding.
6. The specification provides extensive discussion of the late domain of HIV and other viruses, and the critical PT/SAP motif and other late domain motifs, on pages 34-37, and in Figure 1.

As a third matter, the Examiner has further alleged (page 5, 1<sup>st</sup> paragraph) that: “Applicant has not disclosed any specific motif associated with TSG101 that is essential for binding except for the 200 residue N terminal portion.” In response, Applicants note the following:

1. The ubiquitin E2 variant (UEV) domain was found to be present in the N-terminus of Tsg101 and was “defined” by three different research group in 1997 & 1998.
2. Koonin & Abagyan (cited on page 33 of the specification) presented an alignment of a portion of the Tsg101 UEV domain (amino acid residues 13-135) with a variety of ubiquitin-conjugating E2 enzymes in Koonin & Abagyan, *Nat. Genet.* 16:330-331, 1997.
3. Ponting and coworkers used sequence analysis to show the presence of the UEV domain in the N-terminus of Tsg101 and presented their findings in Ponting *et al.*, *J. Mol. Med.* 75:467-467, 1997.

4. Thomson and colleagues present an alignment of amino acid residues 11-153 of Tsg101 with a variety of ubiquitin-conjugating E2 enzymes in Thomson *et al.*, *FEBS Lett.* 423:49-52, 1998.
5. More recently, Pornillos and colleagues used comparative sequence analysis, combined with structural methods (NMR), to define the structurally-ordered UEV domain of Tsg101 as comprising amino acid residues 1-145. See Pornillos *et al.*, *EMBO J.*, 21:2397-2406, 2002.
6. The specification presents data demonstrating that amino acid residues 1-207 of Tsg101 interact with the first 14 amino acid residues of HIV GAGp6 and indicates that this region contains the UEV domain. (Specification, Example 4 and Figures 2, 3 & 4.)
7. The specification also asserts: “the UEV domain of Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions.” (Specification, page 38, lines 5-6.)
8. The specification further asserts: “one interacting partner in the protein complexes can be ... a Tsg101 fragment capable of interacting with HIV GAGp6 (e.g., **a fragment containing the UEV domain of the Tsg101 protein, specifically the amino acid residues 1-207, the amino acid residues 1-147, etc.**)....” (Specification, page 38, lines 24-29; emphasis provided.)

Applicants respectfully submit that in view of what was known in the art at the time the instant application was filed, and in further view of what is disclosed in the specification, there is sufficient written description to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, commensurate with the pending claims.

As a further point, the Examiner has cited *University of California v. Eli Lilly and Co.*, in alleging that the pending claims fail to comply with the written description requirement. Applicants respectfully assert the Federal Circuit ruling in *Univ. Calif. v. Eli Lilly* is **not** relevant to the issue of written description in the instant application, for the following reasons.

In *Univ. Calif. v. Eli Lilly*, the patent at issue (4,652,525; the ‘525 patent) “does not provide a written description of the cDNA encoding human insulin, which is

necessary to provide a written description of the subject matter of claim 5. ... While the example provides a process for obtaining human insulin-encoding cDNA, **there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics**; in other words, it thus does not describe human insulin cDNA. ... No sequence information indicating which nucleotides constitute human cDNA appears in the patent....” *Univ. Calif. v. Eli Lilly*, 43 USPQ2d 1398 (Fed. Cir. 1997); emphasis provided.

Importantly, what was at issue in *Univ. Calif. v. Eli Lilly* is the absolute lack of description of the structural or physical characteristics of the subject matter being claimed (i.e., cDNA encoding human insulin). In particular, claim 5 of the ‘525 patent reads upon a composition of matter (cDNA encoding human insulin) that, at the time the patent application was filed, had not been characterized or described by its “**relevant structural or physical characteristics**” by the Applicants. In contrast, the claims of the instant application read upon compositions of matter (isolated protein complexes) that have been described by both structural and physical characteristics. Specifically, the structural characteristics of the isolated protein complexes have been described by virtue of the fact their constituent proteins (i.e., Tsg101 and HIV GAGp6) had known primary structures at the time the instant application was filed. Further, the physical characteristics of the isolated protein complexes have been described, by the requirement that the constituent proteins interact with one another through specific binding domains in order to form the claimed complex.

Consequently, in contrast to the cDNA encoding human insulin in the ‘525 patent of *Univ. Calif. v. Eli Lilly*, Applicants respectfully assert that appraised of the instant specification, one of average skill in the art would conclude that the claimed subject matter is adequately described, since the claims at issue in the present application read on subject matter that has been defined both by **relevant structural characteristics and relevant physical characteristics**.

Aside from the Federal Circuits’ ruling in *Univ. Calif. v. Eli Lilly*, Applicants note that the Patent Office bears the initial burden of establishing that a specification does not satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and that to meet the required burden, the Office must establish, with a preponderance of

evidence, that a person skilled in the art would not recognize that the inventor had possession of the claimed protein. *See In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). This simply has not been done in the instant case.

With regard to the Examiner's request for "other claimed sequences of GAG late domains, fragments, portions with less than 100% identity," etc., Applicants note that "claimed subject matter need not be described *in haec verba* to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." *In re Herschler*, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979). According to the Federal Circuit, "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

In this respect, Applicants note that several recent decisions by the Board of Patent Appeals and Interferences on nucleic acid and protein claims are illustrative. For instance, in *Ex parte Rachel Meyers*, Appeal No. 2003-1820, Application No. 09/464,039 (BPAI 2004), a claim at issue is drawn in part to an isolated nucleic acid molecule having "a nucleotide sequence encoding a polypeptide having **dehydrogenase activity**, wherein said nucleotide sequence has **at least 70% sequence identity** with the nucleotide sequence set forth in SEQ ID NO:8" (emphasis provided). The Board specifically reversed the Examiner's written description rejection of this claim. The Board agreed with the Applicant that "the claims are limited to nucleotide sequences meeting both the structural requirements of these claims and the claimed functional requirement – having dehydrogenase activity." Given the sequence disclosure (SEQ ID NO:8) in the Meyers Application and the Pfam tool, "a person of ordinary skill in the art at the time the invention was made would recognize the relevant structural characteristics of appellant's

claimed invention that are necessary to place a polypeptide encoded by a nucleic acid variant of SEQ ID NO:8 in the dehydrogenase family of proteins.”

Similarly, in *Ex parte Yuejin Sun*, Appeal No. 2003-1993, Application No. 09/470,526 (BPAI 2004), a claim at issue is directed in part to an isolated “wee1 polynucleotide having at least 80% identity to the coding region of SEQ ID NO:1.” The Board reversed the Examiner’s rejection of the claim under the written description requirement. The specification there did not provide **any** specific example of such polynucleotide other than SEQ ID NO:1. Nevertheless, the Board pointed out that the Federal Circuit has specifically instructed that “[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue.” Because the specification describes (1) the polynucleotide chemical structure SEQ ID NO:1 and the structure of the polypeptide, SEQ ID NO:2, which is encoded by the SEQ ID NO:1, and (2) an example of how to screen for WEE1 activity, the Board held that “such a description in the specification would constitute sufficiently detailed relevant identifying characteristics of the claimed subject matter consistent with *Enzo*.”

Consistent with the Federal Circuit and the Board’s decisions, the PTO’s own Revised Interim Written Description Guidelines Training Materials (hereinafter “Training Materials”) are also instructive. In particular, in Example 14 of the Training Materials, the specification discloses a **single species** of the claimed protein genus. “The specification also contemplates but does not exemplify **variants** of the protein wherein the variant can have any or all of the following: **substitutions, deletions, insertions and additions**. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions **is routine in the art** and provides **an assay for detecting** the catalytic activity of the protein.” *USPTO Revised Interim Written Description Guidelines Training Materials*, page 53 (emphasis provided). The Training Materials holds that the claim in Example 14, which defines a protein variant by (1) sequence identity and (2) its activity (i.e., catalytic activity in this case), meets the written description requirement.

In the instant application under examination, the specification clearly describes that the proteins Tsg101 and HIV GAGp6 interact with each other to form a protein

complex. As noted above, the specification also discloses that “the inventors of the present invention discovered that the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)” (Specification, paragraph bridging pages 34-35, emphasis provided); and “the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions” (Specification, page 38, second paragraph, emphasis provided). The chemical structures of such fragments are clear in view of the GenBank reference numbers provided in Table 1 at page 20, and in further view of the fact that the two proteins were well known in the art at the time the instant invention was made. As any skilled artisan would recognize, the interaction between the proteins HIV GAGp6 and Tsg101, and between the various fragments thereof, is determined by the specific interaction domains that reside within the sequences of such proteins and protein fragments, specifically, the late domain of GAGp6 and the UEV domain of Tsg101. Clearly, sufficiently detailed structural characteristics (the amino acid sequences) and the correlating functional characteristics (binding activities) are disclosed in Applicants’ specification, and these characteristics are consistent with *Enzo*, with the Board’s recent decisions, and with the Training Materials.

As to homologues in particular, they are defined in the claims by (1) percentage identity to either Tsg101 or GAGp6 and (2) binding activity, consistent with Example 14 of the Training Materials, and with the claims in *Ex parte Meyer* and *Ex parte Sun*. The specification also teaches:

Examples of homologues may be the ortholog proteins of other species including animals, plants, yeast, bacteria, and the like. Homologues may also be selected by, e.g., mutagenesis in a native protein. For example, homologues may be identified by site-specific mutagenesis in combination with assays for detecting protein-protein interactions, e.g., the yeast two-hybrid system described below, as will be apparent to skilled artisans apprised of the present invention.”

(Specification, page 12, 1<sup>st</sup> paragraph)

As noted in the Training Materials, methods for generating variants are routine in the art. As generally known to a skilled artisan, substitutions lead to homologues, deletions lead to fragments, while additions result in fusion proteins.

Further, the specification also provides detailed teachings on how to determine or detect the interaction between two polypeptides (e.g., full-length proteins, protein fragments, homologues, and fusion proteins). In other words, the specification describes assays for determining the binding activity of a fragment or homologue or fusion protein of HIV GAG or GAGp6 or Tsg101 (i.e. the binding affinity to the interacting partner). See e.g., Specification, pages 61-75. Indeed, such and other assays for protein-protein interactions are routine and well known in the art.

Therefore, it is submitted that the descriptions provided in the specification constitute sufficiently detailed, relevant identifying characteristics of the claimed subject matter consistent with *Enzo*, and in direct contrast to *Univ. Calif. v. Eli Lilly*. It is also submitted that the instant Office Action has failed to establish why one of ordinary skill in the art, provided with the descriptions of the specification discussed above, would be unable to recognize that the inventor invented and has in possession, the isolated protein complexes of the claims. Accordingly, Applicants respectfully request that written description rejection be reconsidered and withdrawn.

#### **Claim Rejections under 35 USC § 112, 1<sup>st</sup> paragraph – Enablement**

Claims 1-23, 26, 44-50 and 61-64 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action indicates that the specification, while being enabling for GAGp6 (449-500) and TSG101 (7-390), does not reasonably provide enablement for all other fragments, homologues, portions with less than 100% identity, and other GAGs or TSGs. Applicants respectfully traverse, and offer the following arguments.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention without undue experimentation. *Rattheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Enablement is not precluded if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1540, 1555, 220 USPQ 303, 315 (Fed. Cir. 1983). In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a

reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). That is, the Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. *See id.*

As a first matter, Applicants note that the claims under examination are drawn to isolated protein complexes and the application contains extensive teachings on how to express recombinant proteins, determine whether recombinant proteins interact, and make isolated protein complexes. One asserted utility for the isolated protein complexes of the instant invention is that they can be used to create novel drug screening assays designed to identify compounds that disrupt the interaction, thereby potentially disrupting the life cycle of HIV and other viruses.

Perplexingly, in discussing the sufficiency of enablement of pending claims 1-23, 26, 44-50 and 61-64 under 35 USC § 112, first paragraph, the instant Office Action alleges:

The specification does not teach any specific assays that show a novel compound can be discovered using the complex. The specification does not show that novel compounds discovered in the asserted assay will have a useful biological function. There is no showing that novel compounds discovered by using the assay will inhibit HIV budding (or some aspect of HIV infection/replication) in some meaningful way in vitro or in vivo.

(Office Action of March 24, 2005, page 7)

Besides putting the proverbial cart before the horse, Applicants respectfully note that these allegations clearly do not relate to the **enablement** of the specification with regard to the **CLAIMED** invention, since the pending claims under consideration on the merits read upon **isolated protein complexes**, and not upon novel therapeutic compounds, or even methods for selecting such compounds. However, contrary to the allegation of the Examiner, Applicants note that Example 4 (pages 83-84) of the instant application demonstrates that an isolated protein complex of the invention, namely one comprising GST-(HIV-1 GAGp6) interacting with a myc-tagged Tsg101 fragment (residues 1-207), can indeed be used identify compounds that disrupt the interaction between GAGp6 and Tsg101 – as demonstrated by the ability of a 14 amino acid

synthetic peptide to competitively interfere with the interaction of the two fusion proteins.

As a second matter, the instant specification teaches that “the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)” (Specification, paragraph bridging pages 34-35), and that “the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions” (Specification, page 38, second paragraph). In view of these disclosures, and the level of skill in the relevant art, it is clear that one skilled in the relevant arts would know how to make other fragments of the interacting proteins, identify and make homologues of these proteins, and make fragments of the homologues, that would, more likely than not, interact to form a protein complex. For instance, using simple sequence alignment tools, one of skill in the art could readily identify homologues of Tsg101 and/or HIV GAGp6 that contain the requisite binding domains. Further, one of skill in the art could express these homologues, or fragments thereof, as recombinant proteins and test whether they interact with either Tsg101 or HIV GAGp6. Certainly, the Examiner cannot reasonably argue that this is not within the purview of one skilled in the art of molecular biology, since this is what molecular biologists do on a regular basis, using routine experimentation!

With regard to the “Enablement Factors” summarized in *In re Wands*, and recited in the Office Action, Applicants note that there is ample evidence that the level of skill in the art of conducting amino acid sequence alignments, identifying homologous proteins, identifying conserved regions of homologous proteins, making recombinant proteins, detecting protein-protein interactions between recombinant proteins was very high at the time the instant application was filed. Evidence of this high level of skill can be found in the innumerable publications describing, for example, methods of detecting protein-protein interactions that were published prior to the filing of the application. One example of such a publication is the review article by Phizicky and Fields, entitled “Protein-Protein Interactions: Methods for Detection and Analysis” (*Microbiol. Rev.*, 59:94-123, 1995), which was cited within the instant application, and published six years before its filing date.

Additionally, Applicants note that the United States Patent and Trademark Office Board of Appeals has stated:

The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or **if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed** to enable the determination of how to practice a desired embodiment of the invention claimed.

*Ex parte Jackson*, 217 USPQ 804, 807 (1982); emphasis provided.

Towards this end, Applicants note that the specification correctly asserts that “the UEV domain of the Tsg101 protein and the PTAP motif of the HIV GAGp6 are responsible for the interactions” (Specification, page 38, second paragraph). This is all the guidance a skilled artisan would need to practice the invention as claimed, particularly because (a) both Tsg101 and HIV GAGp6 were well characterized proteins known in the art at the time the instant invention was made, and (b) both that the UEV domain of Tsg101, and the late domain of HIV GAGp6, with its vital PTAP motif, were also known in the art at that time. Furthermore, at the time the instant invention was made, methods for detecting protein-protein interactions were well known and routine in the fields of biochemistry and molecular biology. Consequently, it would be apparent to an ordinarily skilled person in the art that, at the time the invention was made, the experimentation required to determine whether a given fragment of Tsg101 interacts with HIV GAGp6, or a particular homologue of GAGp6 interacted with Tsg101, would be routine, and not undue.

To elaborate, at the time the instant invention was made, it was a routine task for a skilled artisan to identify proteins homologous or orthologous to Tsg101 or HIV GAGp6, and to align such proteins so as to identify regions of conservation. It was also routine for a skilled artisan to determine the percentage identity of a given protein relative to Tsg101 or HIV GAGp6, and to recognize whether a particular protein is at least 75% identical to Tsg101, or 50% identical to HIV GAGp6. A skilled artisan could also easily identify regions of homologous proteins showing conservation of amino acid sequence. Moreover, since procedures for making variant proteins with substitutions, deletions, insertions and additions was routine in the art, in combination, such skills would allow a

person of ordinary skill to routinely create recombinant polypeptides at least 75% identical to Tsg101 (i.e., synthetic orthologues), that more likely than not retain the ability to interact with HIV GAGp6, by making changes in amino acid sequence outside of the late domain region. Furthermore, at the time the instant invention was made it was routine for a skilled artisan to determine whether two proteins interact with each other. Applicants' specification contains extensive disclosure in this regard.

What's more, the instant specification also provides specific working examples in which interactions were demonstrated between the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) and the N-terminal 207 residues of Tsg101 (which includes the Tsg101 UEV domain). (*See e.g.*, Specification, Example 4, page 83-84.) Since HIV GAGp6 comprises 52 amino acid residues, and the working example demonstrates that only the first 14 amino acid residues are required for the interaction with Tsg101, the remaining 38 residues (or 73%) are logically not required for the interaction, and are thus potentially amenable to engineered changes, conservative or otherwise. Similarly, since Tsg101 comprises 390 amino acid residues, and the working example demonstrates that, at most, the N-terminal 207 of these residues are required for interaction, the remaining 183 residues (or 47%) are logically not required for the interaction, and are thus potentially amenable to engineered changes, conservative or otherwise. Thus, the specification not only teaches one skilled in the art which amino acid residues of the two proteins are required for their interaction of the two polypeptides, but it also intrinsically teaches which residues can most likely be altered without affecting the interaction between the two proteins.

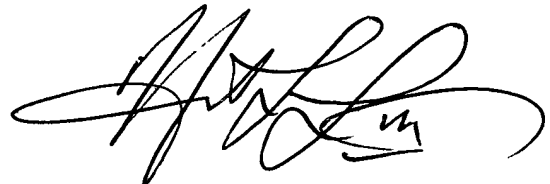
In view of the above, Applicants assert that claims 1-23, 26, 44-50 and 61-64 are fully enabled by the specification in view of: the teachings of the specification, the existence of working examples, the state of the prior art, the nature of the invention, the routine nature of experimentation and, especially, the extraordinarily high level of skill in the relevant art. Consequently, Applicants respectfully request that the enablement rejection be reconsidered and rescinded.

**CONCLUSION**

Applicants believe that once the amendments proposed above have been incorporated into the pending claims, and the arguments presented above are considered, the outstanding rejections will be withdrawn and the pending claims will be in condition for allowance. Consequently, Applicants respectfully request that a timely Notice of Allowance be issued in this case. In order to expedite allowance of this application, the Examiner is invited to telephone the undersigned via his direct office line at 801-883-3463.

A petition for a two-month extension of time is being filed concurrently with this response. Provisions for the payment of the necessary fee have been made in the petition. Therefore, it is believed that no other extension of time, nor any additional fees are due with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any over payment to Deposit Account no. **50-1627**.

Respectfully submitted,



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